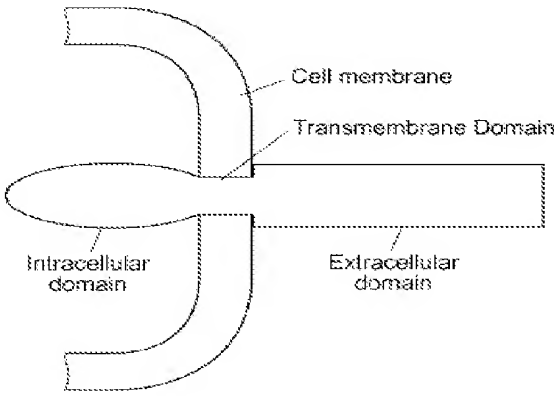
REMARKS

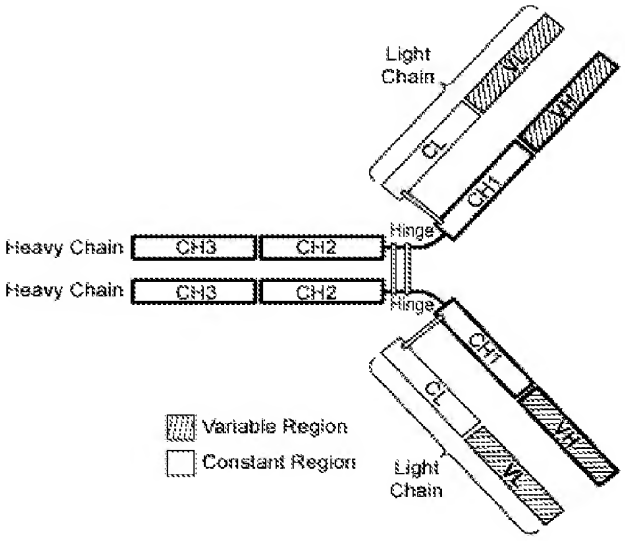
I. Claimed subject matter

The claimed invention relates to a polynucleotide that encodes a fusion protein that combines fragments of two different proteins: a human 75 kD tumor necrosis factor receptor (p75 TNFR), and a human immunoglobulin (antibody).

Two TNF receptors, an approximately 55 kD receptor (p55 TNFR) and an approximately 75 kD/65 kD receptor (p75 TNFR), were known in the art, and the DNA and amino acid sequences for both receptors, as well as the polynucleotide sequences encoding them, had been published before the August 31, 1990 priority date of the present application. Each TNFR contains an extracellular domain that binds TNF, a transmembrane domain that is embedded in the cell membrane, and an intracellular domain. A schematic depiction of a membrane-bound, or "insoluble," TNFR is shown below. The extracellular domain is referred to as a "soluble" fragment because it is not membrane-bound.



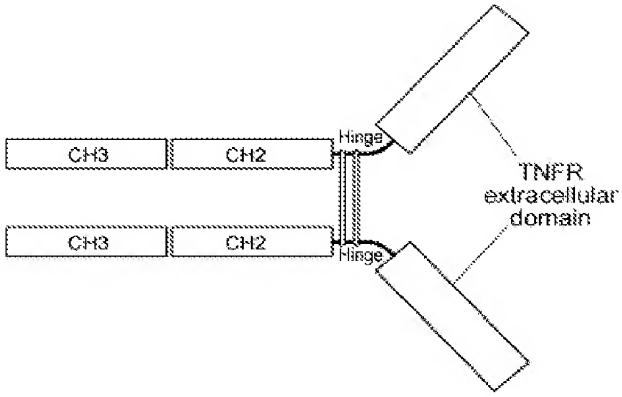
Complete nucleotide and amino acid sequences for human immunoglobulins, including IgG, were also known in the prior art. Immunoglobulins are naturally occurring antibodies composed of multiple amino acid chains. The IgG type of antibody contains two heavy chains and two light chains. Each IgG heavy chain comprises a variable region (VH) and a constant region (CH) composed of the following domains: CH1, hinge, CH2, and CH3 domains. Each light chain comprises a variable region (VL) and a constant region (CL). Each light chain is linked to a heavy chain, and the two heavy chains are covalently linked to each other, by disulfide bonds. A schematic depiction of an IgG immunoglobulin is shown below.



Generally the variable region of an immunoglobulin is responsible for binding antigen, while the constant region is responsible for other functions of immunoglobulins, such as activating antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). Such pro-inflammatory functions are referred to as "effector functions." ADCC includes the recruiting of white blood cells by antibodies bound to a surface antigen and the destruction of the cells or complexes displaying the antigen. ADCC is initiated by antibody binding to antigen and to an Fcγ receptor (FcγR). CDC is a complex, protein-mediated cascade of events that starts with antibody binding to antigen and to protein C1q, ultimately ending with cell lysis.

The claimed polynucleotide constructs encode a fusion protein that combines (a) the soluble, TNF-binding extracellular region of p75 TNFR and (b) all of the domains of the constant region of a human immunoglobulin IgG heavy chain other than the first domain (CH1). The fusion protein is schematically depicted below. Due to the natural cysteine disulfide bonding that occurs between heavy chains in the hinge region, the resulting fusion

protein is homodimeric.



II. Interview Summary

Applicants thank Examiner Schwadron, Supervisory Patent Examiner Shukla, and Quality Assurance Specialist Burke for the in-person interview granted August 4, 2010 to Applicants' representatives Li-Hsien Rin-Laures, Rosemary Sweeney, and Kathleen Fowler. During the interview, Applicants and Examiners discussed the claims presented as new claims 274-280 herein (which correspond to prior claims 233-273), the prior art, and Applicants' previously presented evidence of unexpected results.

Applicants briefly reviewed the claims to p55 TNFR fusion protein claimed in the parent patent, U.S. Patent No. 5,610,279, of which the present application is a divisional. Applicants discussed the application examples showing purification of the p55 and p75 TNFRs from HL60 cells, the examples showing cloning of the full length p55 TNFR cDNA and partial p75 TNFR cDNA, and the examples showing production of an immunoglobulin fusion protein containing (a) the extracellular region of a TNFR and (b) all the domains of an immunoglobulin heavy chain constant region other than the first domain.

Applicants also discussed the timing of the publication of the complete p75 TNFR cDNA and amino acid sequences by Smith *et al.* and by the inventors, relative to Applicants' priority applications. The April 1990 priority application contains the full length p55 TNFR cDNA (Figure 1) and a mostly complete p75 TNFR cDNA sequence (Figure 4) encoding 392 amino acids of the total 461 amino acids of p75 TNFR. In May 1990, Smith *et al.* published the entire p75 TNFR cDNA and amino acid sequence in *Science* 248: 1019-1023, 1990 ("Smith (1990)"). Smith (1990) identified the extracellular, transmembrane and

intracellular regions and noted that they had deposited the p75 TNFR sequence in the widely used public database GenBank. In July 1990, the inventors also published the complete p75 TNFR amino acid sequence in Dembic *et al.*, *Cytokine* 2: 231-237, 1990 ("Dembic"). The Dembic and Smith (1990) amino acid sequences are the same. In the August 1990 European priority application, Applicants added a description of immunoglobulin fusion proteins, Example 11 showing production of an immunoglobulin fusion protein, and a citation to the Smith (1990) publication for its disclosed sequence.

Applicants thank the Examiners for clarifying that there was not a written description rejection with respect to claims reciting SEQ ID NO: 27, the Smith (1990) amino acid sequence. The only issue with respect to SEQ ID NO: 27 was confirming the propriety of the incorporation by reference. As explained in greater detail below, the Examiners reviewed the passages citing Smith (1990) specifically for its disclosure of sequence, the original claims reciting the 75 kilodalton receptor comprising SEQ ID NO: 10, and the original claims reciting immunoglobulin fusion proteins. As noted in the Interview Summary prepared by the Patent Office, agreement was reached that there was intent to incorporate the sequence of the Smith (1990) publication, and that the incorporation by reference was proper. Applicants agreed to repeat in their response the reasons showing the specific intent to incorporate.

Applicants also discussed the written description rejections with respect to claims identifying the known human p75 TNFR by its name, function, molecular weight and 18 amino acids of N-terminal sequence. The Examiners questioned whether the claims encompassed artificial mutants or variants, and Applicants assured the Examiners that the recitation of "human" excluded such mutants and variants. In addition, Applicants discussed claims reciting human p75 TNFR having the same sequence as the p75 TNFR obtainable from HL60 cells, and the Examiner's concern that HL60 cells might mutate over many generations. While no agreement was reached, Applicants offered to insert the ATCC deposit number of the HL60 cells described in the specification and used in the examples.

With respect to obviousness, Applicants discussed the following three main combinations: (a) Smith (1990) and Capon et al., U.S. Patent No. 5,428,130 ("Capon Patent"), (b) Dembic and Capon Patent, and (c) Smith et al., U.S. Patent No. 5,395,760 patent

("Smith Patent") and Capon Patent. Applicants noted that the relevant disclosures of the Smith (1990) and Dembic publications were substantially the same, since both references disclose the complete amino acid sequence of human p75 TNFR and identify the extracellular region. Neither reference discloses immunoglobulin fusions. The Capon Patent discusses a large number of different immunoglobulin fusions but does not disclose p75 or p55 TNFR. The rejection was based on the combination of the extracellular p75 TNFR region disclosed in Smith (1990)/Dembic together with one of the immunoglobulin fragments disclosed in the Capon Patent. With respect to the Smith Patent, Applicants and Examiners discussed its disclosure of an immunoglobulin fusion that is tetrameric (i.e., has two heavy and two light chains) and that includes the CH1 domain of the heavy chain constant region.

The Examiners agreed that it was inappropriate to refuse to consider evidence of unexpected results on the grounds that the results related to encoded protein while the claims related to polynucleotide constructs encoding the protein and methods of making the protein. As noted in the Interview Summary prepared by the Patent Office, the Examiners agreed that Applicants' evidence of unexpected results would be fully considered in the next official action.

As explained in further detail below, Applicants discussed their previously submitted evidence of unexpected results that are relevant to comparing properties of the encoded p75 TNFR fusions to properties of other immunoglobulin fusions, such as CD4-immunoglobulin fusions. Relative to CD4 fusions, the p75 TNFR fusions exhibit improved ligand binding affinity, 1000-fold improved neutralization potency, and markedly reduced effector function (as shown by little or no FcγR-binding in the presence of TNF, and little or no ADCC).

In addition, Applicants discussed their previously submitted evidence of unexpected results that are relevant to comparing properties of p75 TNFR fusions to properties of soluble p75 TNFR fragments consisting of the extracellular region. Relative to the p75 TNFR fragments, the p75 TNFR fusions exhibit 50-fold improved binding affinity, 1000-fold improved potency in neutralizing TNF-mediated cytotoxicity, and altered binding kinetics. Applicants also highlighted the previously submitted declaration of Dr. Lesslauer

regarding the uncertainty that the dimeric TNFR-immunoglobulin fusion protein would even have the correct spatial geometry to bind the TNF trimer.

Finally, Applicants discussed their previously submitted evidence of unexpected results, which are relevant to comparing properties of TNF-binding tetrameric immunoglobulins (containing two heavy chains and two light chains, as well as including the CH1 domain of the heavy chain constant region) to properties of the species of p75 TNFR fusion encoded and produced by the claimed constructs. Relative to tetrameric immunoglobulins, the p75 TNFR fusions of the claims exhibited unique binding properties, a marked lack of aggregation ability, due to an inability to bind two TNF-trimers, a marked reduction in binding to the proteins responsible for initiating ADCC and CDC, and a marked reduction in ADCC and CDC.

Applicants thank the Examiners for their efforts to expedite prosecution by engaging in a preliminary working discussion of the issues that might have been raised had the last office action considered Applicants' evidence of unexpected results. Naturally such a discussion was quite difficult in the absence of a clearly articulated position on the applicability and relevance of the unexpected results, and without the opportunity for the Examiners or Applicants to cite evidence supporting factual assertions. While Applicants agreed to repeat and expand their discussion of unexpected results, and have done their best to try to respond to the issues discussed during the interview, any specific issues if raised in the next office action will necessarily have been newly raised and thus the next office action should be non-final.

III. Information Disclosure Statement

Some documents previously submitted with information disclosure statements ("IDSs") filed on March 2, 2000, December 29, 2004, December 20, 2005 and September 7, 2007 had not been initialed as considered by the Examiner. The SB/08 form submitted on September 7, 2007 had been objected to at pages 32-33 of the outstanding Office Action. This SB/08 has been revised and resubmitted herewith.

The SB/08 form submitted on March 2, 2000 was not initialed by the Examiner. However, all of the documents listed on this SB/08 form are now included on the revised SB/08 form submitted herewith.

Three foreign patent documents listed on the SB/08 filed December 29, 2004 (EP 417563, EP 471701 and JP 01 293024) were not published in English and therefore were not considered by the Examiner. English language counterparts (U.S. patent documents) for each of these references are now listed on the revised SB/08 submitted herewith. In addition, the English language abstract for JP 01 293024 is submitted herewith. Copies of all documents previously submitted are not attached hereto. However, Applicant will provide additional copies if requested. Applicants request that the Examiner provides an initialed copy of the revised SB/08 form.

As discussed during the interview with the SPE and the QAS, Applicants submit herewith an applicant-created form to allow the Examiner to initial that he considered the documents in the IDS filed December 20, 2005. The references submitted with the IDS filed December 20, 2005 are not publications and therefore have no formal title, hence sufficient identifying information was included by identifying them as the Exhibits to the IDS.

Copies of all documents previously submitted are not attached hereto. However, Applicant will provide additional copies if requested. Applicants request that the Examiner provides an initialed copy of all of these forms.

IV. Claim Amendments

Newly added claims 274-280 were discussed during the interview. These claims are nearly identical to previously presented claims that were examined in the June 8, 2010 office action. In addition, the foregoing amendment presents new claims 281-283. These amendments do not add new matter to the application. Applicants presented this reduced claim set in an effort to expedite prosecution by focusing discussion on a limited number of claims. Should claims 274-283 be deemed allowable, Applicants will cancel the remaining claims.

New claim 274 is an independent claim that corresponds to previously presented claim 269. New claim 275 corresponds to previously presented claim 270. New claim 276 corresponds to previously presented claim 269. New claim 277 corresponds to previously presented claim 238. New claim 280 is an independent claim that is nearly identical to previously presented claim 273. The claims have been amended to improve clarity and reduce the number of independent claims, and not for reasons relating to patentability. In addition, the foregoing amendment cancels a number of pending claims without prejudice, and Applicants reserve the right to pursue claims of same or similar scope.

The amendment replacing "isolating" with the synonymous language "purifying" finds support at page 19, lines 13-18 and page 12, lines 1-6. The amendment to add the ATCC deposit number associated with HL-60 cells finds support, e.g. at page 12, line 27, and at page 21, line 28 in the examples.

V. The Rejection Under 35 U.S.C. §132

The insertion of the phrase "incorporated by reference" with respect to the disclosure of SEQ ID NO: 27 in Smith (1990) was rejected as new matter. In addition, the insertion of reference to the plasmid deposited at the American Type Culture Collection (ATCC) under deposit number PTA-7942 was rejected as new matter.

A. Incorporation by reference for Smith (1990) SEQ ID NO: 27

As noted in the Interview Summary prepared by the Patent Office, agreement was reached that there was intent to incorporate the sequence of the Smith (1990) publication, and that the addition of the "incorporation by reference" phrase was proper under 37 CFR §1.57(g)(1). The portions of the specification reviewed by the Examiners during the interview showed that Applicants had a clear intent to incorporate the sequence of Smith (1990), rather than merely referencing it for methodology or background. Thus, the amendment to the specification adds material previously incorporated by reference and is not new matter.

As explained above, prior to the August 31, 1990 priority date of the present application, both Smith *et al.* and the inventors had published the complete amino acid sequence of p75 TNFR, including an identification of the extracellular, transmembrane and

intracellular regions. See Smith (1990), Figure 3, page 1021, and Dembic, Figure 1, page 232. As noted in the Figure 3 legend, Smith *et al.* had deposited the p75 TNFR sequence in the widely used public database Genbank. In the August 31, 1990 European priority application [Exhibit A submitted on November 22, 2006], the inventors added a citation to Smith (1990) specifically for its disclosure of TNF binding protein (TNF receptor) sequence. See page 10, lines 9-10 of the present specification, corresponding to page 6, line 20 of priority application European Pat. Appl. No. 90116707.2.

The Examiners reviewed the passage citing Smith (1990) and the originally filed claims, e.g. claims 5, 16 and 17. The passage is reproduced below:

> In addition thereto, the ***present invention is also concerned with DNA sequences coding for proteins and soluble or non-soluble fragments thereof, which bind TNF***. Thereunder there are to be understood, for example, DNA sequences coding for non-soluble proteins or soluble as well as non-soluble fragments thereof, which bind TNF, such DNA sequences being selected from the following:
>
> (a) DNA sequences as given Figure 1 or Figure 4 as well as their complementary strands, or those which include these sequences;
>
> (b) DNA sequences which hybridize with sequences defined under (a) or fragments thereof;
>
> (c) DNA sequences which, because of the degeneracy of the genetic code, do not hybridize with sequences as defined under (a) and (b), but which code for polypeptides having exactly the same amino acid sequence.
>
> That is to say, ***the present invention embraces*** not only allelic variants, but also those DNA sequences which result from deletions, substitutions and additions from one or more nucleotides of the sequences given in Figure 1 or Figure 4, ***whereby in the case of the proteins coded thereby there come into consideration, just as before, TNF-BP*** [TNF binding proteins]. ***One sequence which results from such a deletion is described, for example, in [Smith et al.,] Science 248, 1019-1023, (1990).***
>
> [Emphasis added; page 9, line 19 to page 10, line 10 of the specification.]

It is clear from the language of this paragraph that "the present invention embraces" the TNF binding protein (TNF receptor) sequence of Smith (1990). During the interview, the Examiners verified that there was only one TNFR sequence described in Smith (1990), so there is no ambiguity regarding the sequence referenced.

In addition, Applicants submit a Declaration of Stewart Lyman, Ph.D. under 37 C.F.R. 1.132 (Exhibit B "Lyman Declaration") which provides further evidence that the skilled artisan would have understood Applicants possessed and meant to incorporate the sequence of Smith (1990). Dr. Lyman states:

> There is a description in the application of the specific full length sequence of the 75 kD TNFR. It is clear from the citation to the Smith (1990) article at page 10, lines 9-10 of the application that the Applicants knew of the Smith (1990) article when they drafted the application and intended to refer to its sequence. [Paragraph 8 of the Lyman Declaration.]

Dr. Lyman furthermore specifically refers to the passage quoted above and concludes:

> One of skill in the art would not have read the application by itself without reference to any other known information. Instead, such a person would have read the application in view of what was known in the art at the effective filing date, particularly in view of the following statements in the application:
>
> > "the present invention embraces . . . One sequence which results from such a deletion is described, for example, in [Smith et al.,] Science 248, 1019-1023, (1990)."
>
> Specification, page 10, lines 3-10. One of skill in the art would also have noted that Dembic *et al. Cytokine* 2(4): 231-7, 1990, published by the same authors as the inventors on the application, disclosed the entire sequence of the mature 75 kD TNFR, which was the same sequence as in Smith (1990), and the same extracellular region (page 232 to page 233, upper left column; and Figure 1 at page 232). Thus, one of skill in the art would have had no doubt that the inventors were in possession of the entire p75 sequence as of August 31, 1990 and that the Applicants clearly intended to incorporate the entire p75 amino

> acid sequence into the specification. [Paragraph 11 of the Lyman Declaration.]
>
> The citation includes the journal name, journal volume, page numbers and year, and thus is a complete citation that uniquely identifies the article. Figure 3 of Smith (1990) discloses the only TNF receptor sequence in this publication, from among the p55 or p75 TNF receptors that are the subject of the application. Thus, the application clearly identifies the reference publication and the application clearly conveys an intent to incorporate by reference the sequences in Smith (1990) of soluble or non-soluble TNF receptors. [Paragraph 13 of the Lyman Declaration]

Thus, as agreed during the interview, the application as filed clearly conveys an intent to incorporate the material by reference, the addition of the "incorporation by reference" phrase was proper under 37 CFR §1.57(g)(1), and the rejection under 35 U.S.C. §132 should therefore be withdrawn.

B. PTA-7942

The Office Action rejected as new matter the insertion of the reference to vector PTA-7942, stating: "Regarding applicants comments and the Lesslauer declaration, the entire sequence of the deposited [PTA-7942] sequence needs to be disclosed and applicant should point out where said entire sequence was described in the specification as originally filed." Page 2 of Office Action.

The requirement for an original disclosure of the entire sequence is clearly erroneous. 37 C.F.R. §1.804(b) permits deposit of biological material such as DNA as long as Applicants "submit a statement from a person in a position to corroborate the fact, stating that the biological material which is deposited is a biological material specifically identified in the application as filed." Applicants have done so by submitting the Third Declaration of Werner Lesslauer Under 37 C.F.R. § 1.132 [Exhibit C submitted on August 30, 2007], which states in paragraph 7 that the DNA sequence within the construct is a DNA sequence identified in the application at page 10, line 34.

Thus, Applicants have satisfied the requirements for biological deposit and the addition of a reference to the deposited plasmid PTA-7942 is proper. The rejection under 35 U.S.C. §132 and corresponding rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

VI. The Rejection Under 35 U.S.C. §112, first paragraph

The Office Action rejected a number of claims for lacking written description under 35 U.S.C. §112, first paragraph. During the interview, the Examiners agreed that there was no written description rejection with respect to claims like claim 280 reciting the extracellular domain of SEQ ID NO: 27.

A. Human p75 TNFR comprising SEQ ID NO: 10

The claims were rejected for assertedly "encompass[ing] sequences other than that disclosed in Fig. 4." Page 3 of Office Action. The Office Action states that "[t]he only nucleic acid encoding a sequence comprising soluble portions of insoluble TNF binding proteins of a TNF 75 kD receptor disclosed in the specification are those disclosed in the Figures." Page 4 of Office Action. The rejection inappropriately relied on several Federal Circuit cases in which the claimed sequences had not yet been determined, stating:

> The court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans [citing *Regents of the Univ. of California v. Eli Lilly and Co.,* 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995)] at 1240. In the instant case, the specification has disclosed a single nucleic acid encoding a 55 kD TNF receptor with the nucleic acid sequence disclosed in Figure 1. The Federal Circuit has held that if an inventor is 'unable to envision the detailed constitution of a gene so as to distinguish it from other materials . . . conception has not been achieved until reduction to practice has occurred' [citing *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.,* 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991)]. [Pages 4-5 of Office Action.]

This rejection is factually and legally flawed because the complete p75 TNFR amino acid sequence had been determined and was known in the art as of August 31, 1990.

Contrary to statements in the Office Action, the specification discloses a p75 TNFR sequence other than the sequence of Fig. 4. As explained above, the specification's citation to the sequence of Smith (1990) is a disclosure of the complete p75 TNFR amino acid sequence.

The cases cited in the Office Action, such as *Regents v. Lilly*, and *Amgen v. Chugai*, do not apply. The present situation differs from those cases in two important aspects. First, Applicants are not attempting to claim a broad genus such as vertebrate DNA. The present claims recite "human". Second, the human p75 TNFR DNA sequence was well known in the art, having been disclosed in two different journal articles, *i.e.,* Smith (1990) and Dembic, as well as the GenBank database (as stated in Smith (1990)). It is well settled that "[w]hat is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." MPEP §2163(II)(A)(3)(a), citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986) and *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 U.S.P.Q.2d 1078, 1085 (Fed. Cir. 2005).

It would be clear legal error for the Examiner to require the specification to reproduce a sequence that was already known in the art. MPEP §2163(II)(A)(3)(a) states that "***there is no* per se *rule*** that an adequate written description of an invention that involves a biological macromolecule ***must contain a recitation of known structure***" [quoting *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 U.S.P.Q.2d 1001, 1007 (Fed. Cir. 2006) (emphasis added)]. In Falkner, the Federal Circuit stated that "we hold that where, as in this case, ***accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences*** (here 'essential genes'), satisfaction of the ***written description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences***." *Falkner*, 448 F.3d at 1368, 79 U.S.P.Q.2d at 1008.

In this case, as in Falkner, the relevant DNA and amino acid sequences were known in the art. Thus, reiteration of known sequences should not be required to satisfy the written description requirement. Moreover, even though Falkner explicitly states that incorporation by reference is not required, the application does incorporate by reference the sequence of Smith (1990), SEQ ID NO: 27. See the discussion in section II above and the Interview Summary prepared by the Patent Office.

MPEP §2163(II)(A)(3)(a) also cites *Capon*, 418 F.3d at 1358, 76 U.S.P.Q.2d at 1084 [emphasis added], stating "'The ***Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure*** or formula or chemical name for the nucleotide sequences of the claimed chimeric genes' ***where the genes were novel combinations of known DNA segments***." In Capon, the claims related to DNA encoding chimeric proteins comprising the variable region of an immunoglobulin fused to the transmembrane and cytoplasmic portions of a receptor. The claims in Capon, like the claims of the instant application, are also related to chimeric proteins. In Capon, which was an interference, the Board rejected both parties' claims for lack of written description because no chimeric DNA sequence was recited in the respective specifications. *Id.* at 1355. On appeal, both parties argued that their invention was the novel combination of DNA segments known in the art, not the discovery of the DNA segments themselves, and that re-analysis of known sequences was not required. *Id.* at 1356. The Federal Circuit reversed the Board's decision, holding that the Board erred by requiring the specification to reiterate known prior art sequences. *Id.* at 1358.

The present facts are directly parallel to both Capon and Falkner. In this case, as in Capon, the invention is the novel combination of known sequences. Thus, it is error to require the specification to reproduce the known full-length sequence of the human p75 TNFR.

B. HL-60 cells and SEQ ID NO: 10

The Office Action asserted that there is no support for sections (b) and (c) of claim 125 and sections (b) and (c) of claim 233. Since claim 125 is cancelled, this aspect of the rejection is obviated. Claim 233 recites that (b) the TNFR amino acid sequence is the same as that encoded by a nucleic acid from HL-60 cells, and (c) the TNFR amino acid sequence comprises the amino acid sequence of SEQ ID NO: 10. Page 3 of Office Action.

Applicants note that originally filed claim 8 was directed to a p75 TNFR comprising SEQ ID NO: 10. Examples 2-6 describe the purification of the 65/75 kD TNF receptor from HL-60 cells identified by ATCC Deposit No. CCL 240 (page 21, line 28 of the specification). Example 7 at page 33 of the specification describes sequencing of this approximately 75 kD receptor, and demonstrates that its N-terminal sequence is SEQ ID NO:

10. Thus, the specification describes a human 75 kD TNF receptor having all of the characteristics (a), (b) and (c) set forth in claim 233.

Applicants previously submitted evidence that SEQ ID NO: 10, which is 18 amino acids in length, uniquely identifies the 75 kilodalton human TNF receptor. A 2006 search of the GenBank "All non-redundant GenBank CDS" database with SEQ ID NO: 10 produced identical matches only with sequences that are p75 TNFR sequences. See Exhibit D [Submitted August 30, 2007]. If that was true even as late as 2006, it would have been true in 1990 when the application was filed.

C. Asserted "spontaneous mutation" of HL-60 cells

The claims were also rejected for "encompass[ing] use of HL60 cDNA libraries from any HL60 cell line," assertedly because DNA from different HL-60 lines will differ "due to spontaneous mutation." Page 3 of Office Action. However, the Monnat reference cited in the Office Action characterizes the forward mutation rate as "comparatively low." See, e.g. the abstract. In Monnat, HL-60 cells were selected for 6-thioguanine (TG) resistance; analysis of the TG-resistant cells revealed a mean forward mutation rate to TG resistance of 1.7 to 6 x 10^{-7}/cell/generation.

Nevertheless, solely to expedite prosecution, Applicants have omitted reference to HL-60 cells from new claim 277, and have amended claim 233 to identify the particular HL-60 cell line described in the specification at page 12, line 27, deposited under ATCC No. CCL 240. Example 2 at page 21, line 28 confirms that ATCC No. CCL 240 is the HL-60 cell line described in the working examples.

Applicants submit herewith evidence that the ATCC avoids the possibility of spontaneous mutation after many passages (generations) of cell lines, since the ATCC takes care to supply all of its cell lines at a low passage number. See page 6 of the ATCC brochure attached as Exhibit E. Applicants also submit herewith evidence that the ATCC supplies the HL-60 cells deposited under ATCC No. CCL 240 between passage 8 and 21. [Exhibit F page 20 right column of Fleck *et al. Clin. Vaccine Immunol.* 12: 19-27, 2005].

For all of these reasons discussed above in section III, the various rejections under 35 U.S.C. §112, first paragraph, should be withdrawn.

VII. The Rejection Under 35 U.S.C. §103

The Examiner rejected the claims as assertedly obvious under 35 U.S.C. §103 in view of a variety of combinations of art: (1) Smith et al., *Science* 248: 1019-1023, 1990 ("Smith (1990)") and Capon et al., U.S. Patent No. 5,428,130 ("Capon Patent"), (2) Smith et al., U.S. Patent No. 5,395,760 ("Smith Patent"), and Capon Patent, (3) Dembic et al., *Cytokine* 2: 231-237, 1990 ("Dembic") and Capon Patent, and (4) Smith Patent, Hohmann et al., *J. Biol. Chem.* 264: 14927-14934, 1989 ("Hohmann") and Capon Patent.

Smith (1990) and Dembic were relied upon for essentially the same teaching of DNA encoding the extracellular region of p75 TNFR. The Capon Patent was relied upon for its teaching of immunoglobulin fusion proteins. The Smith Patent was relied upon for its teaching of DNA encoding the extracellular region of p75 TNFR and for its disclosure of a specific type of tetrameric immunoglobulin fusion protein, a "chimeric antibody molecule". Hohmann was cited for teaching that HL60 cells express p75 TNFR.

For convenience, combinations (1) and (2) will be discussed together, and combinations (3) and (4) will be discussed together.

A. Smith (1990) or Dembic in view of Capon Patent

Smith (1990) was cited for its teaching of DNA encoding p75 TNFR having the amino acid sequence of SEQ ID NO: 27. Smith (1990) was also cited for teaching the extracellular portion of the p75 TNFR. The Examiner acknowledged that Smith (1990) does not teach fusions with immunoglobulin. See page 6 of the Office Action.

Dembic, the inventors' own publication, was cited for its teaching of DNA encoding p75 TNFR derived from HL60 cells that comprises the various peptide fragments recited in the claims. Dembic was also cited for teaching the extracellular portion of the p75 TNFR. The Examiner acknowledged that Dembic does not teach fusions with immunoglobulin domains. See page 8 of the Office Action.

The Capon Patent was cited for teaching DNA encoding immunoglobulin (Ig)/ligand binding fusion proteins. The patent was also cited for teaching that "the DNA encoding the Ig portion of the fusion protein can contain at least the hinge, CH2 and CH3 domains of the constant region of an Ig heavy chain." Office Action at pages 7 and 8; Capon Patent, col. 10, 2nd paragraph. The Capon Patent does not teach TNFR as the source of the ligand binding portion of the Ig fusion protein. However, the Examiner concluded that the claimed invention is obvious and motivated because Smith (1990) and Dembic each teach the p75 TNFR, and "Capon *et al.* teach that the ligand binding portion of the Ig/ligand binding fusion protein can be derived from a wide variety of different known cell surface receptors. . ." Office Action at pages 6, 7, and 9.

1. No prima facie case of obviousness

The rejection did not articulate an adequate rationale motivating the selection of the particular homodimeric fusion proteins encoded and produced by the claimed constructs, from among the many types of fusion proteins disclosed in the Capon Patent. Column 12, line 1 to column 14, line 40 of the Capon Patent displays over one hundred different species of immunoglobulin fusions, all of which appear to include the entirety of the heavy chain constant region (CH) and/or the light chain constant region (CL). The selection of a species from a large genus disclosed in a prior art reference can be nonobvious. *See In re Baird*, 16 F.3d 380, 382-83, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994).

The Capon Patent discloses fusion of receptor fragments to immunoglobulin fragments of varying lengths and with varying conformations, including monomeric, homodimeric, heterodimeric, trimeric, tetrameric, homomultimeric and heteromultimeric forms. [Col. 11, lines 1-35, col. 11, lines 52-55, col. 13, lines 18-21.] The disclosed fusions can contain a variety of immunoglobulin constant region fragments, such as the entire constant region (CH1-hinge-CH2-CH3), hinge-CH2-CH3, CH2-CH3, or the light chain constant region (CL). [Col. 10, lines 19-25.]

There are many possible species even among the homodimeric fusion proteins described. Example 5 of the Capon Patent at col. 44, lines 59-62 describes an immunoglobulin fusion protein in which a portion of the hinge region, as well as the CH1

domain, is deleted. The Capon Patent also claims a hybrid immunoglobulin that "comprises a functionally active CH1 domain". Claim 14 of the Capon Patent. In contrast, the claimed constructs encode all of the domains of the constant region of an IgG heavy chain other than CH1.

In a preferred embodiment, given the trimeric nature of the TNF ligand, one of ordinary skill in the art might well have preferred a monomeric form, such as TNFR-CH2-CH3, because one would have expected the monomeric form to bind TNF with greater certainty of success. Dimeric or other multimeric forms may have had a spatial geometry that prevented high affinity binding to the trimeric TNF ligand. Appellants previously submitted evidence supporting the uncertainty of binding, in the form of a Declaration Under 37 C.F.R. 1.132 of Dr. Werner Lesslauer (Exhibit G "Lesslauer Declaration A" submitted on December 9, 2004).

Lesslauer Declaration A describes the basis for the uncertainty that the spatial configuration of the dimeric TNFR fusion protein would allow it to bind a trimeric TNF ligand:

> . . . knowledge of the spatial structure of TNFα was available. In the relevant protein crystal, TNFα was present in the form of a trimer, and it was hypothesized that this was not only a result of the crystallization but that instead, the TNFα trimer is the biologically active form as well. But the spatial geometry of the receptor binding site was unknown. Thus, it could have been possible that the fusion with IgG fragments created a spatial structure that would have contained TNF receptor sequences but which, due to its spatial structure, was completely unable to bind TNFα.

The steric distances between the two TNF-binding sites in the dimer and the degree of flexibility required to accommodate the TNF trimer were unknown. Moreover, there was uncertainty that the TNFR portion of the fusion protein would retain the three-dimensional structure of its TNF-binding site when fused to a relatively large immunoglobulin heavy chain fragment, especially after recombinant production in a host cell.

Thus, there is a good rationale for selecting a monomeric p75 TNFR-immunoglobulin fusion in order to maximize likelihood of binding to trimeric TNF. Deletion

of the hinge region, which is responsible for disulfide bonding and resulting dimerization of the protein, would also have been desirable from the standpoint of eliminating a part of the constant region involved in the pro-inflammatory effector functions. The ordinary skilled artisan would have been motivated to avoid combining such pro-inflammatory activity with an anti-inflammatory TNF-binding agent such as soluble p75 TNFR.

Thus, a proper *prima facie* case of obviousness has not been established because a particular species of the many forms of fusion proteins described in the Capon Patent is encoded by Applicants' claimed polynucleotides, and no rationale for selecting this species has been advanced by the Examiner. Instead, Applicants have shown a rationale for selecting a different, monomeric species from among the many species of fusion proteins disclosed in the Capon Patent. For this reason, among other reasons discussed below, the claimed invention represents a nonobvious selection of species.

2. *Unexpected Results*

Unexpectedly superior properties, unexpectedly different properties, and the absence of expected properties are all relevant factors that can rebut an obviousness rejection. "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness... No set number of examples of superiority is required." MPEP §716.02(a)(II), citing *In re Chupp*, 816 F.2d 643, 646, 2 U.S.P.Q.2d 1437, 1439 (Fed. Cir. 1987). Moreover, the "[p]resence of a property not possessed by the prior art is evidence of nonobviousness." MPEP §716.02(a)(III), citing *In re Papesch*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). Finally, the "[a]bsence of property which a claimed invention would have been expected to possess based on the teachings of the prior art is evidence of unobviousness." MPEP §716.02(a)(IV), citing *Ex parte Mead Johnson & Co.*, 227 U.S.P.Q. 78 (Bd. Pat. App. & Inter. 1985).

Similarly, where the prior art would have predicted no improvement in an activity, an improvement in activity constitutes a novel and unexpected property. *In re Corkill*, 711 F.2d 1496, 1499, 226 U.S.P.Q. 1005, 1008 (Fed. Cir. 1985); *In re Chupp*, 816 F.2d at 646. In some cases, an improvement in activity may be so marked that it may be

classified as a different property entirely. See *In re Waymouth*, 499 F.2d 1273, 1276, 182 U.S.P.Q. 290, 293 (C.C.P.A. 1974).

Note that an "applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art." MPEP §716.02(e)(III) (citing *In re Geiger*, 815 F.2d 686, 689, 2 U.S.P.Q.2d 1276, 1279 (Fed. Cir. 1987) (Newman, J., concurring). Moreover, Applicants are *not* required to compare their claimed invention with the embodiment (extracellular p75 TNFR-hinge-CH2-CH3 fusion protein) assertedly suggested by the combination of references relied upon. As stated in MPEP §716.02(e)(III), "[r]equiring applicant to compare claimed invention with polymer [embodiment] suggested by the combination of references relied upon in the rejection of the claimed invention under 35 U.S.C. 103 'would be requiring comparison of the results of the invention with the results of the invention'" (citing *In re Chapman*, 357 F.2d 418, 422, 148 U.S.P.Q. 711, 714 (C.C.P.A. 1966)).

Such a comparison (comparing the invention with itself) has been rejected as improper and impossible by the Board in *Ex parte Hunt*, Appeal No. 2009-009337, December 11, 2009 (Bd. Pat. App. & Int.). The Board explained:

> The operative question, when evaluating proffered evidence of unexpected results, is *not* whether a composition, which did not exist in the prior art, would have certain properties if it was made. The ***question is, would a skilled worker have expected a claimed composition to have the properties alleged to be unexpected, based on what was known in the prior art before the composition was actually made?*** [Emphasis added; *Ex parte Hunt*, slip op., page 9.]
>
> That is, the Examiner's approach to the issue would require a patent applicant to show that a claimed composition has superior properties *when compared to itself*, an obvious impossibility. The correct standard is, does the claimed composition have unexpectedly superior properties *when compared to the closest composition existing in the prior art*? [Emphasis in original; *Ex parte Hunt*, slip op., pages 9-10.]

Regardless of whether the Smith (1990)/Dembic references or the Capon Patent are considered the closest prior art, Applicants have provided overwhelming evidence of unexpected results in several different categories.

a. Comparison relative to the soluble, extracellular region of p75 TNFR of Smith (1990) or Dembic

Both Smith (1990) and Dembic were cited for teaching the complete DNA and amino acid sequences of p75 TNFR and for teaching the extracellular domain of p75 TNFR. Page 6 of Office Action (Smith (1990)); page 8 of Office Action (Dembic). The Examiner acknowledged that no immunoglobulin (Ig) fusions were described in either reference. Smith (1990) suggests that "soluble, recombinant forms of this [p75 TNF] receptor may also be produced to explore the clinical value of TNF inhibition in pathological settings." Page 1022, 2nd col.

Evidence of record that is discussed below shows that, when properties of p75 TNFR fusions are compared to properties of soluble, recombinant forms of p75 TNFR, unexpected results are observed in a variety of categories. Relative to the soluble p75 TNFR fragments, p75 TNFR-IgG1 hinge-CH2-CH3 fusions encoded by the claimed invention exhibits 50-fold improved binding affinity and 1000-fold improved potency in neutralizing TNF-mediated cytotoxicity. Soluble p75 TNFR fragments fused to the hinge region of IgG3 also exhibit improved binding kinetics and potency compared to soluble p75 TNFR fragments alone. These results are all the more surprising in view of Lesslauer Declaration A, which explains the uncertainty that the dimeric TNFR-Ig fusion protein would even have the correct spatial geometry to bind the TNF trimer.

In prior art regarding other Ig fusions, such as CD4-Ig fusions, fusion of the soluble CD4 fragments to human Ig heavy chain constant regions had no effect on binding affinity or potency. Capon, *Nature*, 337:525-531,1989 ("Capon (1989)") states that the "dissociation constant (K_d) for the interaction of each immunoadhesin [Ig fusion] with gp120, calculated by Scatchard analysis (Fig. 3*a*, inset) was ***indistinguishable from that of soluble rCD4*** . . . [emphasis added]." Page 526, 2nd col.; also Table 1 at page 527. Capon (1989) also states that "[b]oth CD4 immunoadhesins blocked cell killing with the ***same potency as soluble rCD4***. . ." Page 529, 2nd col.

In contrast, a fusion protein consisting of the extracellular domain of p75 TNFR fused to all of the domains of an IgG1 heavy chain constant region other than CH1, (i.e., hinge, CH2 and CH3 domains) exhibited an unexpected ***50-fold*** improvement in binding affinity for TNF and a dramatic ***1000-fold*** improvement in TNF neutralizing potency *in vitro* compared to the extracellular domain of p75 TNFR alone. Mohler *et al.*, *J. Immunol.*, 151:1548-1561, 1993 (Exhibit I "Mohler"). Fig. 1 at page 1550 depicts the structure of the dimeric Ig fusion protein (sTNFR:Fc) and the soluble, monomeric, extracellular portion of p75 TNFR (sTNFR); see also page 1557, 2nd col. Figure 2A at page 1551 demonstrates the approximately 50-fold increase in binding affinity of the Ig fusion compared to the sTNFR, as measured by the percent inhibition of TNF-binding between radiolabeled recombinant TNF-α and U937 cells expressing surface p80 and p60 (i.e., p75 and p55) TNFR. Figure 2B at page 1551 demonstrates the 1000-fold more potent TNF neutralization capacity of the Ig fusion compared to the sTNFR, as measured in a TNF-induced cytotoxicity assay of L929 cells.

The 1000-fold increase in TNF neutralizing potency observed for the p75 TNFR fusion protein encoded by the claimed invention was even higher than would have been predicted on the basis of the 50-fold increased binding affinity, and therefore is of a completely unexpected magnitude that renders the increased potency a different property altogether. See *In re Waymouth*, 499 F.2d 1273, 1276, 182 U.S.P.Q. 290, 293 (C.C.P.A. 1974) (marked improvement may be "classified as a difference in kind [of property], rather than one of degree").

Similarly, Lesslauer Declaration A (Exhibit G) shows that a fusion of soluble p75 TNFR to all of the domains of an IgG3 heavy chain constant region other than CH1 exhibited unexpectedly higher kinetic stability (how long the complexes remain bound before dissociating) and improved inhibition of TNF activity. Kinetic stability is demonstrated by the figure on page 3 of the declaration, which states that "TNFα dissociated with considerably slower kinetics from p75 TNFR/IgG than it does from p75sTNFR." Superior TNF neutralization is shown in the table on page 4 of the declaration, which states that "compared to the soluble extracellular domain p75sTNFR, the fusion protein p75sTNFR/IgG causes a surprisingly superior neutralization of the TNF activity . . ."

Where the prior art would have predicted no improvement in binding properties or potency for the p75 TNFR fusion protein encoded by the polynucleotides of instant claims as compared to the soluble extracellular domain of p75 TNFR alone, the observations of improved binding properties and dramatically increased potency for fusion protein encoded and produced by the claimed constructs constitute novel and unexpected properties that render the claimed invention nonobvious.

b. Comparison relative to other Ig fusion proteins of Capon Patent

The Capon Patent was cited for "teach[ing] DNA encoding [immunoglobulin] Ig/ligand binding fusion proteins" and that "the Ig portion of the fusion protein can contain at least the hinge, CH2 and CH3 domains of the constant region of an Ig heavy chain." Page 6 of Office Action. While the Capon Patent did not teach TNFR as a source for the ligand binding portion of the fusion protein, the Examiner asserted that the patent teaches that the ligand binding portion can be derived from a wide variety of cell surface receptors. Page 7 of Office Action.

When the properties of the p75 TNFR fusion protein encoded and produced by the claimed constructs are compared to those of other dimeric Ig fusions, such as the CD4-Ig fusions described in Example 5 of the Capon Patent (at col. 44, line 55), the fusions exhibit (i) unexpectedly improved TNF binding affinity, 1000-fold improved TNF neutralization potency, and improved binding kinetics, and (ii) unexpectedly reduced effector functions as shown by FcγR binding, C1q binding, ADCC and CDC. Moreover, compared to other dimeric binding molecules, the p75 TNFR fusion proteins encoded by the claimed polynucleotides exhibit a surprising absence of aggregation ability and unique 1:1 binding stoichiometry.

i. Improved binding properties and potency

As explained immediately above in section IV.A.2.a., when the properties of the p75 TNFR fusion protein encoded by the claimed constructs are compared to those of other Ig fusions, such as the CD4-Ig fusions described in Example 5 of the Capon Patent (at col. 44, line 55), the p75 TNFR fusion proteins exhibit unexpectedly improved TNF binding affinity, 1000-fold improved TNF neutralization potency, and improved binding kinetics.

ii. Markedly reduced effector functions

In addition, the p75 TNFR fusions encoded and produced by the claimed constructs exhibit markedly reduced or nearly absent effector function (as shown by FcγR binding, C1q binding, and *in vitro* assays of ADCC and CDC) relative to other Ig fusion proteins. The Capon Patent teaches that its hybrid immunoglobulin fusion proteins were expected to retain immunoglobulin effector functions, such as ADCC and CDC. See, e.g., col. 4, lines 45-49 ("It is a further object to provide novel hybrid immunoglobulin molecules which combine the adhesive and targeting characteristics of a ligand binding partner with immunoglobulin effector functions such as complement binding, cell receptor binding and the like.").

Ig fusions that retain at least the hinge and CH2 domains of the Ig would have been expected to retain effector functions. It was well known that the binding sites for the proteins that initiate ADCC and CDC (FcγR and C1q, respectively) were within the CH2 domain or between the hinge and CH2 domains of the heavy chain constant region. See, e.g., Capon [Exhibit J *Nature* 337: 525-531, 1989 ("Capon (1989)"]:

> Two major mechanisms for the elimination of pathogens are mediated by the Fc portion of specific antibodies. Fc activates the classical pathway of complement, ultimately resulting in lysis of the pathogen, whereas binding to cell Fc receptors can lead to ingestion of the pathogen by phagocytes or lysis by killer cells. The ***binding sites for Fc cell receptors and for the initiating factor of the classical complement pathway, C1q, are found in the constant region of heavy chain (the CH2 domain for C1q and the region linking the hinge to CH2 for Fc cell receptors***). ***We aimed to incorporate both of these functions into the immunoadhesins*** [i.e. Ig fusion proteins]. [Capon (1989), page 528, 1st col.; emphasis added.]

Evidence of record shows that other Ig fusions, such as CD4/IgG fusions, retained both ADCC and CDC activities. *Byrn et al.* (*Nature* 344: 667-670, April 1990, Exhibit H) shows that a fusion protein in which CD4 is fused to the hinge region of human IgG1 constant region (missing the CH1 domain) retains ADCC activity. Figure 1 at page 668 shows the structure of the Ig fusion. Byrn states that "CD4 immunoadhesin mediates ADCC towards HIV-infected, but not uninfected, CEM human T-lymphoblastoid cells in a dose-dependent manner (Fig. 2a and b). Soluble recombinant (rCD4) does not mediate ADCC."

Page 668, 1st col.; see also Fig. 2 at page 669. Similarly, Traunecker, *Nature*, 339:68-70, 1989 (Exhibit K "Traunecker") shows that a fusion protein in which CD4 is fused to the hinge region of murine IgG2 (Fig. 1 at page 68) also retains ability to bind FcγR and C1q, the proteins that mediate the initiation of ADCC and CDC, respectively (page 69, 1st col. and Fig. 3).

Evidence of record shows that a p75 TNFR fusion protein encoded by the claimed constructs exhibits markedly reduced or nearly absent effector functions. See Kohno *et al.*, Presentation 1495, poster 271 presented at American College of Rheumatology Annual Meeting, November 13-17, 2005, San Diego, CA (Exhibit L "Kohno"); Khare *et al.*, Poster 715 presented at the Annual Meeting of the Society for Investigative Dermatology (SID), May 3 -5, 2006, Philadelphia, PA (Exhibit M "Khare"); Barone *et al.*, *Arthritis Rheum.*, v42(9) supplement, September 1999 (S90) (Exhibit N "Barone").

The fusion protein designated as etanercept in Kohno, Khare and Barone consists of the extracellular domain of p75 TNFR fused to all of the domains of an IgG1 heavy chain constant region other than CH1. Etanercept is produced recombinantly in CHO cells, which are host cells conventionally used to produce immunoglobulins with full effector functions. (See Hu *et al.*, Overview of Cell Culture Technology[1] at, pages 5 and 6 and Natsume *et al. Drug Design Dev. Ther.* 3: 7-9, 2009 at page 7; Enbrel US Product Insert ; Exhibits O, P, and Q respectively). Kohno, Khare and Barone show that etanercept unexpectedly exhibited drastically reduced, if not completely eliminated, effector function. In the presence of TNF, etanercept bound only weakly to FcγR or C1q, proteins that mediate the initiation of ADCC and CDC, respectively. See Figures 8 and 9 of Kohno. Etanercept also exhibited little to no ADCC and markedly reduced CDC. See Figures 3 and 4 of Khare. In the same assays, a control TNF-binding immunoglobulin designated infliximab bound strongly to FcγR and C1q in the presence of TNF, and mediated both ADCC and CDC as assayed *in vitro*. Figures 8 and 9 of Kohno; Figures 3 and 4 of Khare. Barone also reported that etanercept could not mediate complement-dependent killing of cells that express TNF.

[1] Hu et al. Overview of Cell Culture Technology at https://hugroup.cems.umn.edu/NTU/NTU%202010/Lecture%20notes/Cell%20Culture%20Processes/Overview.pdf (last visited Sept. 1, 2010)

As noted in Smith (1990), a valuable property of the soluble TNFR is its potential for TNF inhibition in disease settings. Similarly, as noted in Applicants' specification, a use of the TNFR fusions encoded by the claimed constructs is to treat inflammatory disorders, by inhibiting or reducing the pro-inflammatory effects of TNF. See page 12, lines 17-21 and page 20, lines 15-18 of the specification. Therefore, the marked reduction in the pro-inflammatory effector functions of the immunoglobulin portion of the fusion protein is beneficial in the treatment of inflammatory disorders, where promoting inflammation is undesirable.

Thus, against the expectation in the art as of the application's effective filing date that Ig fusions would retain pro-inflammatory immunoglobulin effector functions (FcγR binding, C1q binding, ADCC and CDC), the near absence or significant reduction in effector functions observed for the p75 TNFR fusion protein encoded and produced by the claimed constructs are each unexpected and advantageous properties that render the claimed invention nonobvious.

The present situation is highly analogous to the case of *In re May*:

> Claims directed to a method of effecting analgesia without producing physical dependence by administering the levo isomer of a compound having a certain chemical structure were rejected as obvious over the prior art. Evidence that the compound was unexpectedly nonaddictive was sufficient to overcome the obviousness rejection. Although the compound also had the expected result of potent analgesia, there was evidence of record showing that the goal of research in this area was to produce an analgesic compound which was nonaddictive, enhancing the evidentiary value of the showing of nonaddictiveness as an indicia of nonobviousness.

MPEP 716.02(c)(I), citing *In re May*, 574 F.2d 1082, 197 U.S.P.Q. 601 (C.C.P.A. 1978).

Similarly, in the present case, even if one assumes for the sake of argument that the TNF-binding capability of the Ig fusion encoded and produced by the claimed constructs was an expected result, the significantly reduced pro-inflammatory effector functions are beneficial and unexpected results sufficient to overcome the obviousness rejection.

iii. Unique binding properties evidenced by absence of aggregating ability and 1:1 binding stoichiometry

In addition, the dimeric p75 TNFR fusions encoded by the claimed polynucleotides exhibit an absence of the aggregating ability that would be expected for dimeric binding partners that bind to multimeric ligands such as trimeric TNF. Evidence of record, Larsson *et al., FEBS Lett.* 98:333-338, 1979 (Exhibit R "Larsson") illustrates this general principle that dimeric products form aggregates with multimeric ligand, while monomeric products do not. Larsson shows that dimeric NAD prepared by covalently linking two NAD compounds (bis-NAD) aggregated with and precipitated the tetrameric enzyme lactate dehydrogenase (LDH) in the classic Ouchterlony double diffusion test. See Figure 3 at page 337. In this test, ligand (LDH) is placed in the center well of an agarose gel and the ligand binding partners (bis-NAD, monomeric NAD or control) are placed in peripheral wells that are equidistant from the center well. As the ligand and ligand binding partner diffuse towards each other, they bind and aggregate, causing visible precipitation lines to form in the agarose gel. In Figure 3 of Larsson, visible precipitation lines are seen for wells 1-3 (containing bis-NAD) but not for wells 4-6 (containing monomeric NAD or buffer only).

Evidence of record demonstrates that the p75 TNFR fusions encoded by the claimed polynucleotides lack this expected aggregating ability. Figure 6 of Kohno shows the results of an Ouchterlony test of three different multimeric TNF binding partners: two different anti-TNF antibodies, and etanercept, an Ig fusion protein consisting of the extracellular domain of p75 TNFR fused to all of the domains of an IgG1 heavy chain constant region other than CH1. The anti-TNF antibodies formed high molecular weight aggregates and a precipitation line when combined with TNF, while etanercept ***did not aggregate or precipitate***. Etanercept's lack of ability to aggregate with TNF is surprising because etanercept, like the bis-NAD of Larsson, is divalent. One would have predicted that a divalent TNF binding molecule would form aggregated complexes with the naturally trimeric TNF ligand.

The lack of ability to aggregate is likely due to the unusual 1:1 binding stoichiometry. Kohno shows that a primarily 1:1 binding stoichiometry was observed in the

presence of excess TNF (Figure 2), while a 2:1 etanercept:TNF complex was formed in the presence of excess etanercept (Figure 5). No complexes were observed in which one molecule of etanercept bound two TNF trimers. In contrast, Figures 3 and 4 show that, in the presence of TNF, the antibodies adalimumab and infliximab produced aggregated complexes (in which 3 or more antibodies bind 3 or more TNF trimers) of 600,000 to 4,000,000 molecular weight and 800,000 to 14,000,000 molecular weight, respectively. The proposed binding models are depicted schematically in Figure 7 of Kohno.

The absence of an ability to form aggregated complexes with multiple TNF trimers is an unexpected result that is advantageous in treating inflammatory and other disorders. For example, physical proximity of IgG molecules, such as occurs in aggregated complexes, plays an important role in complement activation, which is undesirable in inflammatory disorders. Further, deposition of antigen:antibody aggregates (also called immune complexes or antigen-antibody complexes) in tissue sites was recognized in the art to be pathogenic. Type III hypersensitivity reactions, serum sickness and autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis were believed to be the result of such immune complexes. *Fundamental Immunology*, 2nd ed., Paul, ed., Raven Press, New York, 1989, at pages 679-701; *Immunology*, 1st ed., Klein ed., Blackwell Scientific Publications, Boston, 1990, pp. 446-447. (Exhibits S and T, respectively)

Thus, against the expectation in the art as of the application's effective filing date that dimeric TNFR Ig fusion proteins would form aggregated complexes with TNF, the lack of ability to aggregate and unexpected 1:1 binding stoichiometry is an unexpected and advantageous property that renders the claimed invention nonobvious.

When considered and given due weight, Appellants' evidence of unexpected results in a multitude of different categories rebuts any possible case of obviousness and requires reversal of the rejection under 35 U.S.C. §103. "[W]hen an applicant demonstrates *substantially* improved results . . . and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary." *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995)(emphasis in original).

B. Smith Patent and Capon Patent, optionally combined with Hohmann

The Smith Patent was cited for its teaching of DNA encoding p75 TNFR of SEQ ID NO: 27 and for teaching the extracellular portion of the p75 TNFR. The Smith Patent was also cited for assertedly teaching DNA encoding an immunoglobulin (Ig) fusion molecule. The Examiner acknowledged that the Smith Patent does ***not*** teach a fusion protein wherein the immunoglobulin protein ***lacks the CH1 domain***. Page 7 of Office Action. Hohmann was cited for teaching that HL60 cells express p75 TNFR. Page 10 of Office Action.

The Examiner concluded that the claimed invention is obvious and motivated because the Smith Patent teaches the p75 TNFR and Ig fusion proteins, and "Capon *et al.* teach that the ligand binding portion of the Ig/ligand binding fusion protein can be derived from a wide variety of different known cell surface receptors. . ." Page 8 of Office Action.

1. No prima facie case of obviousness

There is no *prima facie* case of obviousness because one does not arrive at the claimed invention by combining the Smith Patent with the Capon Patent. The primary focus of the Smith Patent is the cloning of p75 TNFR DNA (Example 2), and the expression of various soluble fragments in Examples 3-8. While the Smith Patent contemplates conjugates and fusion proteins, none were made. There is no rationale for selecting the chimeric antibody molecules, in particular, from among the variety of conjugates of TNFR described, which include tandem repeats joined by a linker, as well as conjugates to polymer, polyethylene glycol, dextran, biotin-avidin, dinitrophenol and trinitrophenol:

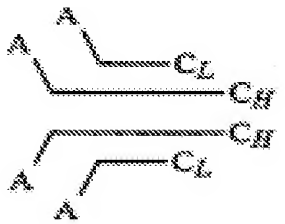
> Other derivatives of TNF-R within the scope of this invention include covalent or aggregative conjugates of TNF-R or its fragments . . . . [Col. 7, lines 44-46]
>
> Both monovalent forms and polyvalent forms of TNF-R are useful . . . For example, a bivalent soluble TNF-R may consist of two tandem repeats of amino acids 1-235 of FIG. 2A [the extracellular domain], separated by a linker region. Alternative polyvalent forms may also be constructed, for example, by chemically coupling TNF-R to any clinically acceptable carrier molecule, a polymer selected from the group consisting of Ficoll, polyethylene glycol or dextran using conventional coupling techniques. Alternatively, TNF-R may be chemically

> coupled to biotin, and the biotin-TNF-R conjugate then allowed to bind to avidin, resulting in tetravalent avidin/biotin/TNF-R molecules. TNF-R may also be covalently coupled to dinitrophenol (DNP) or trinitrophenol (TNP) and the resulting conjugate precipitated with anti-DNP or anti-TNP-IgM, to form decameric conjugates with a valency of 10 for TNF-R binding sites.
>
> A recombinant ***chimeric antibody molecule*** may also be produced having TNF-R sequences substituted for the variable domains of either or both of the immunoglobulin molecule heavy and light chains and ***having unmodified constant region domains.*** For example, chimeric TNF-R/IgG1 may be produced from two chimeric genes – a TNF-R/human κ light chain chimera (TNF-R/Cκ) and a TNF-R/human γ1 heavy chain chimera (TNF-R/Cγ -1). [Col. 10, lines 33-61; emphasis added.]

Even if, for the sake of argument, one assumes selection of the tetrameric chimeric antibody molecule described in the Smith Patent, combining that disclosure with the Capon Patent does not arrive at the claimed invention. The ordinary skilled artisan reading the two cited references would select the chimeric antibody molecules described in the Capon Patent that are very much like those described in the Smith Patent. The Capon Patent states:

> Those compositions of this invention, particularly those in which a ***biologically active portion of a ligand binding partner is substituted for the variable region of an immunoglobulin chain***, are believed to exhibit improved in vivo plasma half life. . .The hybrid immunoglobulins of this invention are also ***constructed in a fashion similar to chimeric antibodies*** in which a variable domain from an antibody of one species is substituted for the variable domain of another species. [Col. 15, lines 9-25.]

See, for example, the tetramer schematic at col. 11, lines 15-20, reproduced below:



The rejection has thus failed to articulate a rationale for why the ordinary skilled artisan would have selected homodimeric Ig fusions, which are unlike the tetrameric Ig fusions (chimeric antibody molecules) described in the Smith Patent that contain two light chains in addition to the two heavy chains.

The rejection has also failed to provide a rationale for why the ordinary skilled artisan would ignore the teaching of chimeric antibody molecules having "unmodified constant region domains" in the Smith Patent that motivates the selection of an Ig fusion that comprises the CH1 domain. Col. 10, line 57 of Smith Patent. In view of this teaching, one would select an embodiment of the Capon Patent which has unmodified constant region domains. The Capon Patent explicitly states that one of its ***preferred*** embodiments is a fusion protein that has unmodified heavy and light chain constant region domains, because the ligand binding partner is substituted for the variable region of the immunoglobulin .

The relevant portion of the Capon Patent states:

> In a ***preferred embodiment*** in which the stable plasma protein is an immunoglobulin chain, the ligand binding partner will be substituted into at least one chain, and ordinarily for the variable region of the immunoglobulin or suitable fragment thereof. [Col. 5, lines 37-41]

MPEP §2144.08 states that the Examiner is obligated to "consider any teaching or suggestion in the reference of a ***preferred species or subgenus that is significantly different in structure from the claimed species or subgenus***. Such a teaching may weigh against selecting the claimed species or subgenus and thus against a determination of obviousness." MPEP §2144.08(II)(A)(4)(c) (citing *In re Baird*, 16 F.3d at 382-83). For example, MPEP §2144.08 cites *Baird* for the example that "teachings of preferred species of a complex nature within a disclosed genus may motivate an artisan of ordinary skill to make similar complex species and thus teach away from making simple species within the genus." MPEP §2144.08(II)(A)(4)(c) (citing *In re Baird*, 16 F.3d at 382).

In the primary reference relied upon, the Smith Patent, the only immunoglobulin fusions disclosed are tetrameric chimeric antibody molecules that include two entire heavy chain constant regions and two entire light chain constant regions. The

Smith Patent thus teaches away from Applicants' selection of homodimeric Ig fusions that have no light chains at all. Moreover, the Smith Patent teaching of "unmodified constant regions" teaches one to prefer an embodiment that comprises the CH1 domain. Thus, the cited art teaches away from the particular species of Ig fusion proteins encoded and produced by the claimed constructs, which consist of the extracellular region of p75 TNFR and "all the domains of an immunoglobulin heavy chain constant region other than the first domain."

For all of these reasons, no *prima facie* case of obviousness has been established because there was no reason to select the species of Ig fusions encoded by the claimed polynucleotides from among the multitude of Ig fusions described in the Capon Patent or the multitude of TNFR conjugates described in the Smith Patent

2. Unexpected Results

As noted above, unexpectedly different properties and/or the absence of expected properties are all relevant factors that can rebut an obviousness rejection. This "[e]vidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims." MPEP §716.02(b)(III) (citing *In re Boesch*, 617 F.2d 272, 276, 205 U.S.P.Q. 215 (C.C.P.A. 1980)).

The focus of the Smith Patent is the cloning of p75 TNFR and soluble fragments of the receptor (see Examples 2-6). As explained above in section VI.A.2.b.ii., Applicants' evidence shows that, when properties of the fusions encoded by the claimed constructs are compared to those of soluble p75 TNFR fragments, the p75 TNFR fusions exhibit unexpectedly 50-fold improved TNF binding affinity, unexpectedly 1000-fold improved TNF neutralizing potency, and improved binding kinetics.

The immunoglobulin fusion proteins described in the Smith Patent were hypothetical and never actually made, and "applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art." MPEP §716.02(e)(III). Moreover, for the reasons described immediately above, the tetrameric chimeric antibody molecules disclosed in the Smith Patent are very different from the species of Ig fusion proteins encoded by the claimed polynucleotides. They are tetrameric, they include two light

chains that are absent from the homodimeric fusion proteins recited in the claims, and moreover include two CH1 domains.

Nevertheless, as discussed below, evidence of record shows that, when properties of a chimeric antibody molecule analogous to the chimeric antibody molecules disclosed in the Smith Patent are compared to properties of the p75 TNFR fusions encoded and produced by the claimed constructs, unexpected results are observed in a variety of categories. "Evidence of unexpected properties may be in the form of a direct or indirect comparison." MPEP §716.02(b)(III). The p75 TNFR fusions encoded by the claimed polynucleotides exhibited unique binding properties, lack of aggregation ability, due to an inability to bind two TNF-trimers, markedly reduced binding to the proteins responsible for initiating ADCC and CDC, nearly absent ADCC and markedly reduced CDC.

The chimeric antibody molecules of the Smith Patent are structurally very analogous to the anti-TNF antibody infliximab. Table 1 below compares the components of the chimeric antibody molecules described at col. 10, line 53 of the Smith Patent with the components of infliximab. Both are tetrameric. Both contain two heavy chain constant regions and two light chain constant regions. The heavy chain constant regions of both include CH1, hinge, CH2 and CH3 domains. In both, the natural variable regions of the human antibody have been replaced with different TNF-binding regions.

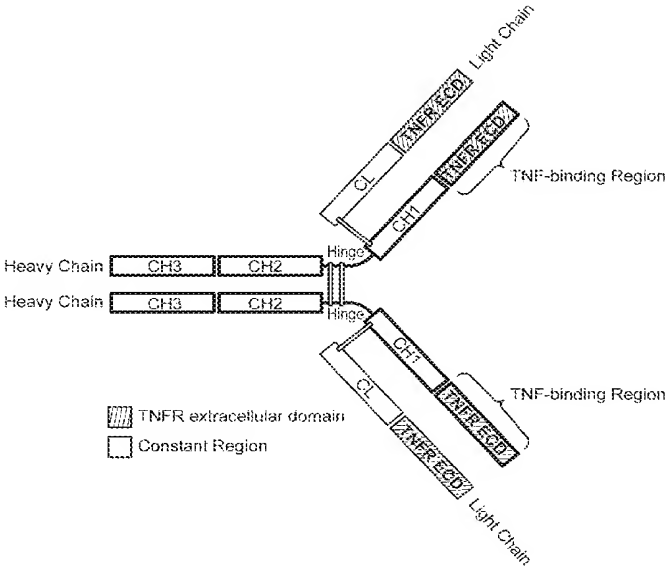
Table 1

	Smith Patent	Infliximab	Etanercept
Tetrameric	X	X	
Dimeric			X
TNF-binding region	X	X	X
Light chain constant region	X	X	
CH1	X	X	
Hinge, CH2, CH3	X	X	X
IgG1 (claim 276)	X	X	X

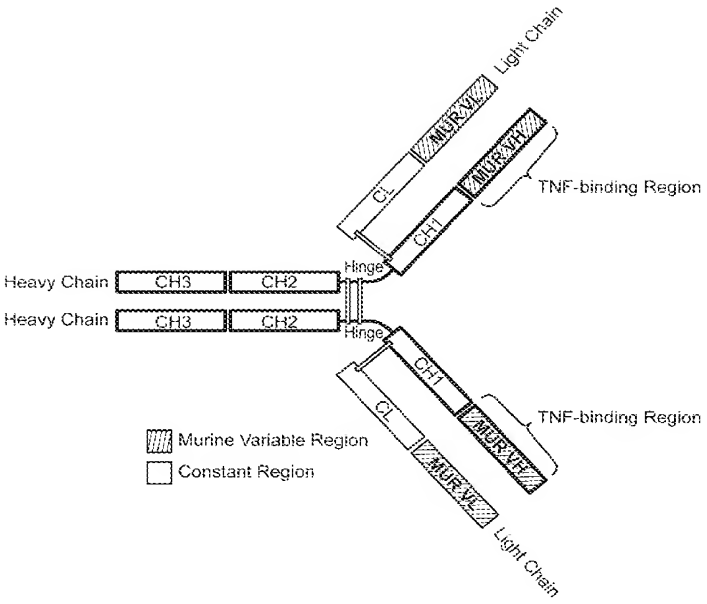
In fact, the only difference between the chimeric antibody molecules of the Smith Patent and infliximab is in the TNF-binding regions. The Smith Patent teaches replacing the approximately 110-amino-acid natural variable regions of an antibody with TNF-R sequences, which might include the soluble fragments described in Examples 3-5

(amino acids 1-163, 1-185 or 1-235 of p75 TNFR). See col. 10, lines 58-61. Infliximab is a chimeric antibody molecule in which the natural variable regions of the human antibody have been replaced with murine variable regions. (See page 23 Remicade Product Insert, Exhibit U) The molecules are depicted schematically below.

Smith Patent:



Infliximab:



When the properties of infliximab, a molecule analogous to the chimeric antibody molecules of the Smith Patent, are compared to the properties of a species of p75 TNFR fusion encoded by the claimed polynucleotides, a number of unexpected results are observed. As described above in section VI.A.2.b.ii., the fusion protein designated as etanercept in Kohno, Khare and Barone has markedly reduced FcγR-binding and C1q-binding in the presence of TNF, and exhibits markedly reduced or nearly absent ADCC and CDC. Figures 8 and 9 of Kohno; Figures 3 and 4 of Khare. Etanercept is produced recombinantly in CHO cells, which are host cells conventionally used to produce immunoglobulins with full effector functions. (See Hu *et al.*, Overview of Cell Culture Technology[2] at, pages 5 and 6 and Natsume *et al.* Drug Design Dev. Ther. 3: 7-9, 2009 at page 7; Exhibits O and P, respectively).

In contrast, Kohno and Khare show that infliximab bound strongly to FcγR and C1q in the presence of TNF, and mediated both ADCC and CDC. Figures 8 and 9 of Kohno; Figures 3 and 4 of Khare. While the TNF-binding variable regions of infliximab

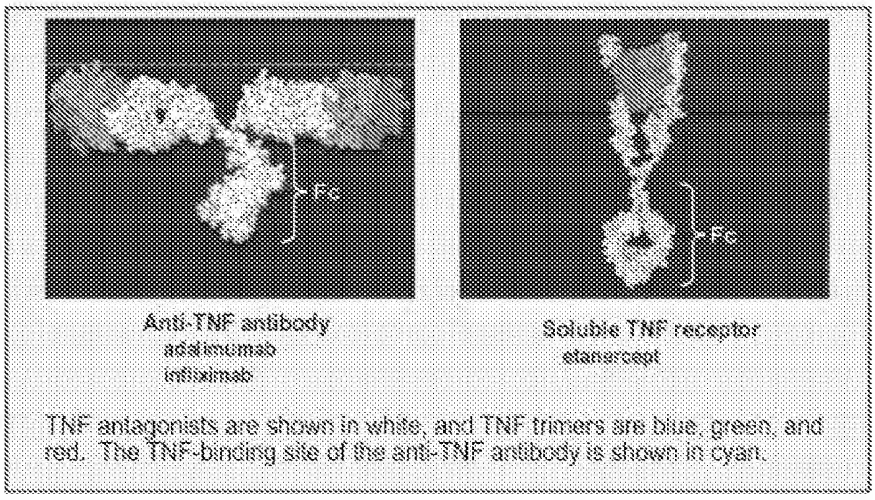
[2] Hu et al. Overview of Cell Culture Technology at https://hugroup.cems.umn.edu/NTU/NTU%202010/Lecture%20notes/Cell%20Culture%20Processes/Overview.pdf (last visited Sept. 1, 2010)

differ from the TNF-binding regions of etanercept, the constant regions of both are derived from IgG1. It has been explained above in section VI.A.2.b.ii. that the heavy chain *constant region*, not the variable regions, mediates the effector functions of an immunoglobulin.

Moreover, as described above in section VI.A.2.b.iii., the fusion protein designated as etanercept in Kohno lacks the aggregation ability expected of a dimeric binding molecule and exhibits a unique 1:1 binding stoichiometry. Figures 1 and 5 of Kohno. In contrast, infliximab forms high molecular weight aggregates (in which 3 or more antibodies bind 3 or more TNF trimers), of 800,000 to 14,000,000 molecular weight, respectively. Figure 4 of Kohno. The proposed binding models are depicted schematically in Figure 7 of Kohno.

Proposed models showing the differences in the binding interactions of TNF trimer with a tetrameric TNF-binding fusion protein, compared to a dimeric TNF-binding fusion protein, are depicted in Figure 1 of Kohno reproduced below. The white molecule on the left represents the tetrameric anti-TNF antibody infliximab, which is shown as binding to two colored TNF trimers; each arm binds to a different TNF trimer. The white molecule on the right represents etanercept; a single TNF trimer fits within and binds to both arms.

Figure 1. Models of TNF Antagonists bound to TNF



Thus, the claimed invention results in a homodimeric protein that has very different tertiary structure and different binding stoichiometry with the TNF trimer, as illustrated by the hypothetical models above (see Figures 1 and 5 of Kohno).

When considered and given due weight, Appellants' evidence of unexpected results in a multitude of different categories rebuts any possible case of obviousness and requires reversal of the rejection under 35 U.S.C. §103. The evidence shows that the p75 TNFR-Ig fusions encoded and produced by the claimed constructs exhibit unique binding properties, affinity and potency that would not have been expected, and that the immunoglobulin fragments encoded by the claimed polynucleotides exhibit completely different effector properties than those predicted by the prior art.

Supreme Court case law requires that Applicants' claimed invention be deemed nonobvious where, as here, evidence shows that the asserted combination of prior art elements are not carrying out their established functions. "When considering obviousness of a combination of known elements, the operative question is thus 'whether the improvement is more than the predictable use of prior art elements according to their established functions.'" MPEP §2141(I), citing *KSR Intl' Co. v. Teleflex, Inc.* 550 U.S. 398, 417, 82 U.S.P.Q.2d 1385, 1396 (2007).

CONCLUSION

In view of the foregoing amendments and remarks, Applicants believe the pending claims are in condition for allowance and early notice of thereof is requested.

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Respectfully submitted,

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EXHIBIT LIST

Exhibit	Document	Submitted on	Submitted with
A	1990 European priority application	November 22, 2006	Supplemental ADS
B	Declaration of Stewart Lyman Ph.D. under 37 C.F.R. § 1.132	Herewith	
C	Third Declaration of Werner Lesslauer under 37 C.F.R. § 1.132	August 30, 2007	Amendment and Response to Office Action
D	SEQ ID NO: 10 GenBank Search Results	August 30, 2007	Amendment and Response to Office Action
E	ATCC Brochure	Herewith	
F	Fleck *et al. Clin. Vaccine Immunol. 12: 19-27, 2005*	Herewith	
G	Lesslauer Declaration A	December 9, 2004	Amendment and Response to Incomplete Reply to Restriction Requirement
H	Byrn, *Nature*, 344:667-670, April 1990	August 30, 2007	Amendment and Response to Office Action
I	Mohler *et al. J. Immunol.*, 151:1548-1561, 1993	August 30, 2007	Amendment and Response to Office Action
J	Capon *Nature* 337: 525-531, 1989	August 30, 2007	Amendment and Response to Office Action
K	Traunecker, *Nature*, 339:68-70, 1989	August 30, 2007	Amendment and Response to Office Action
L	Kohno *et al.* Presentation 1495, poster 271 presented at American College of Rheumatology Annual Meeting, November 13-17, 2005, San Diego, CA	August 30, 2007	Amendment and Response to Office Action
M	Khare *et al.*, Poster 715 presented at the Annual Meeting of the Society for Investigative Dermatology (SID), May 3 -5, 2006, Philadelphia, PA	August 30, 2007	Amendment and Response to Office Action
N	Barone *et al.*, *Arthritis Rheum.*, v42(9) supplement, September 1999 (S90)	August 30, 2007	Amendment and Response to Office Action
O	Hu et al. Overview of Cell Culture Technology	Herewith	
P	Natsume *et al.* Drug Design Dev. Ther. 3: 7-9, 2009	Herewith	
Q	Enbrel US Product Inert	Herewith	
R	Larsson *et al., FEBS Lett.* 98:333-338, 1979	August 30, 2007	Amendment and Response to Office Action

Exhibit	Document	Submitted on	Submitted with
S	*Fundamental Immunology*, 2nd ed., Paul, ed., Raven Press, New York, 1989, at pages 679-701	August 30, 2007	Amendment and Response to Office Action
T	*Immunology*, 1st ed., Klein ed., Blackwell Scientific Publications, Boston, 1990, pp. 446-447	August 30, 2007	Amendment and Response to Office Action
U	Remicade Product Insert	Herewith	